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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/750,005

12/30/2003

Herbert T. Nagasawa

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05/01/2006

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EXAMINER

HEARD, THOMAS SWEENEY

ART UNIT

PAPER NUMBER

1654

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/750,005

Applicant(s)

NAGASAWA ET AL.

Examiner

Thomas S. Heard

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50 and 51 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50 and 51 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>3/16/2006</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

The Applicants Amendments to the claims received on February 27, 2006 is acknowledged.

The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action.

Claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51 are currently pending. Claims 5, 6, 8, 11-19, 23, 24, 27-32, 36, 37, 40-45, 48, 49, and 52-104 have been cancelled by the Applicants.

Rejection and objections not addressed in this office action with regard to the previous office action mailed October 19, 2005 are hereby withdrawn.

Claim Rejections - 35 USC § 103

Applicant's arguments filed February 27, 2006 have been fully considered but they are not persuasive.

Claims 1-4, 7, 9, 10, 20-22, 25-26, 33-35, 38, 39, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Demopoulos et al, US Patent 6,159,500 and Eriksson, Stellan A. and Bengt Mannervik, The Reduction of the L- cysteine-Glutathione Mixed Disulfide in Rat Liver, FEBS Letters, March 1970, 74(2):26-8.

Applicants have termed the naturally occurring thiol of GHS, that of GSSG, a sulfhydryl protected glutathione. Applicants have argued that '500 patent does not

suggest that GSH can be replenished by a GSH ester, but that they are expensive and toxic. Applicants are claiming an ester so the Examiner is not sure of why this argument is being presented. The fact that the GSH is being administered with ascorbic acid as a stabilizer is also off point as many drugs require chemical stabilization to be an effective formulation. Applicant's have argued that the '500 patent does not suggest replenishment of GSH by a sulfhydryl protected glutathione. This is not true as column 1 and lines 30-34, it is clearly stated that GSH is **produced** from oxidized glutathione (GSSG), strongly stating that GSSG is a precursor to GSH. Therefore, that argument that sulfhydryl protected glutathione prodrug (the naturally occurring oxidized glutathione) is capable of replenishing GHS is invalid.

Applicants have argued that the Examiner's rational and application as prior art of the reference Eriksson, et al, The Reduction of the L-cysteine-Glutathione Mixed Disulfide in Rat Liver, FEBS Letters, March 1970, 742):26-8 is not suggested in the prior art. The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on

legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

Eriksson, et al teaches that CySSG is in equilibrium with GSSG, thus demonstrating that all components are capable of being replenished through the addition of any of the four forms taught by Demopoulos et al, see the results section where $\text{CySSG} + \text{GSH} = \text{CySH} + \text{GSSG}$ is figured. Applicants have argued that GSH produces GSSG and '500 argues that GSSG produces GSH. Both are true as this is what Eriksson et al is stating in the above chemical equation. Applicants have argued that L-Cysteine is not a prodrug, which is true, but irrelevant to the argument. The naturally occurring GSSG is not a prodrug either because the body (liver) makes it and if the body (liver) makes it how can it be a prodrug? No matter the fact that L-Cysteine is not a prodrug and has to be administered in a different ("prodrug") form, the administration of any "prodrug" form of L-Cysteine that will in turn be released into its free form, will couple with GSSG and produce GSH, thereby reducing oxidative stress.

It would have been obvious at the time of the invention to use the compounds of glutathione, (GSH), oxidized glutathione (GSSG), mixed disulfide with cysteine (CySSG), to replenish the intracellular concentration of such an important small molecule. Given the rapid distribution of GHS in the plasma and the bodies (cells)

Art Unit: 1654

ability to recycle GSSG and CySSG, any one of the four forms of glutathione would be capable of raising the intracellular concentration of the needed glutathione. It would be obvious to use any glutathione precursor that is capable of raising the glutathione levels in any disease. One would be motivated to do given Demopoulos et al teaching of the benefits and importance of glutathione in the management of oxidative states of the cell and it's role in disease states. Therefore, the invention as a whole is prima facie obvious over the prior art.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

Art Unit: 1654

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TSH

A handwritten signature in black ink, appearing to read "Bruce Campell". The signature is fluid and cursive, with the first name "Bruce" and last name "Campell" clearly distinguishable.

**BRUCE R. CAMPPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600**